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(54) Title: METHOD FOR PREPARING CUCURBITURILS

(57) Abstract: The invention relates to a method for preparing cucurbiturils. The method comprises reacting an oligomer consisting of 2 to 11 linked glycolurils or glycoluril analogues with one or more compounds selected from glycoluril, glycoluril analogues and/or oligomers of glycoluril or glycoluril analogues, in the presence of an acid, to form a cucurbituril. The method can be used to prepare variably substituted cucurbiturils having specific substituted units at specific locations in the cucurbituril. The invention also provides cucurbiturils prepared by the method of the invention. The invention further provides novel cucurbiturils.

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METHOD FOR PREPARING CUCURBITURILS

## FIELD OF THE INVENTION

The present invention relates to a method for preparing  
5 cucurbit[4 to 12]urils.

## BACKGROUND TO THE INVENTION

Cucurbiturils are a class of macrocyclic compounds based  
on oligomers of glycoluril or glycoluril analogues.

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"Cucurbituril" is the name given to the cyclic oligomer  
formed by linking six (6) glycoluril molecules via  
methylene bridges. However, the term "cucurbituril" has  
also been used, and is used in this specification, to  
15 refer to a class of compounds. To avoid confusion, the  
compound cucurbituril is referred to in this specification  
as "unsubstituted cucurbit[6]uril".

Unsubstituted cucurbit[6]uril was first described in the  
20 literature in 1905 in a paper by R. Behrend, E. Meyer and  
F. Rusche (Leibigs Ann. Chem., 339, 1, 1905). The  
macrocyclic structure of unsubstituted cucurbit[6]uril was  
first described in 1981 by W.A. Freeman et. al.  
("Cucurbituril", J. Am. Chem. Soc., 103 (1981), 7367-  
25 7368). Unsubstituted cucurbit[6]uril has a chemical  
formula of  $C_{36}H_{36}N_{24}O_{12}$  and is a macrocyclic compound having  
a central cavity.

The substituted cucurbituril decamethylcucurbit[5]uril was  
30 first synthesised and identified in 1992 by Flinn et. al.  
(Angew. Chem. Int. Ed. Engl., 1992, 31, 1475).

Various unsubstituted and substituted cucurbit[4 to  
12]urils were synthesised by Day et. al. as described in  
35 the applicant's international patent application no.  
PCT/AU00/00412 (WO 00/68232), incorporated herein by  
reference.

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WO 00/68232 describes the preparation of various cucurbit[4 to 12]urils from glycoluril, substituted glycolurils, or a mixture of glycoluril and substituted glycolurils. WO 00/68232 also describes the preparation of cucurbit[4 to 12]urils from a diether analogue of glycoluril, or a mixture of a diether analogue of glycoluril and glycoluril (Example 2 and Example 122). All the methods for preparing cucurbit[n]urils described in WO 00/68232 comprise reacting glycoluril and/or one or more glycoluril analogues to form the cucurbituril.

A class of cucurbit[4 to 20]urils and methods for preparing these cucurbit[4 to 20]urils are also described in US patent no. 6,365,734. All the methods for preparing cucurbit[4 to 12]urils described in US patent no. 6,365,734 comprise reacting glycoluril to form unsubstituted cucurbit[4 to 20]urils, or reacting substituted glycoluril to form substituted cucurbit[4 to 20]urils where all the units of the formula (B) as defined below making up the cucurbit[4 to 20]uril are identical.

Most of the cucurbiturils described in the prior art are unsubstituted or uniformly substituted cucurbiturils, that is, cucurbiturils where all the units of the formula (B) as defined below making up the cucurbituril are identical. The methods for preparing cucurbiturils described in WO 00/68232 can be used to prepare "variably substituted cucurbiturils" as defined below. If the methods for preparing cucurbit[n]urils described in WO 00/68232 are used to prepare "variably substituted cucurbiturils" as defined below, a large number of different variably substituted cucurbiturils are typically produced. For example, in Example 122(2) of WO 00/68232 cucurbit[s,u]urils were formed where s and u are 1,4; 2,3; 3,2; 4,1; 1,5; 2,4; 3,3; 4,2; 5,1; 1,6; 2,5; 3,4; 4,3; 5,2; 6,1.

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Cucurbit[n]urils comprise a rigid central cavity with two portals to the central cavity. These portals are surrounded by polar groups and are narrower in diameter  
5 than the internal diameter of the cavity.

Cucurbit[4 to 12]urils selectively complex various molecules. For example, the central cavity selectively encapsulates gases and volatile molecules. Cucurbit[4 to  
10 12]urils can also selectively form complexes with molecules at the polar ends of the central cavity. Cucurbit[4 to 12]urils can be used to form complexes with, and then later release, gases, volatiles, and other molecules. These properties give cucurbit[4 to 12]urils a  
15 wide variety of uses. These uses include for example:

- entrapment and removal of pollutants,
- use as odourisers, releasing fragrances slowly over time,
- to trap unpleasant odours or toxic vapours, and  
20 ▪ chemical purification or separation techniques, for example, in chromatographic columns.

It would be advantageous to provide alternative methods for preparing cucurbit[4 to 12]urils.  
25

#### SUMMARY OF THE INVENTION

The present inventors have found that for many uses of cucurbit[4 to 12]urils, it is desirable to use "variably  
30 substituted cucurbiturils", that is, cucurbit[4 to 12]urils in which the units of the formula (B) as defined below making up the cucurbituril are not identical.

The inventors have found that the number and type of groups at  $R^1$ ,  $R^2$ ,  $R^3$  and/or  $R^5$  in the units of the formula  
35 (B) making up the cucurbit[4 to 12]uril, and the relative location of those groups within the cucurbituril, alters

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the solubility of the cucurbituril. For example, tetramethylcucurbit[2,4]uril has greater solubility in water than unsubstituted cucurbit[6]uril. The inventors have also found that the number and type of groups at R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and/or R<sup>5</sup> in the units of the formula (B) making up the cucurbit[4 to 12]uril affects the extent to which the cucurbituril forms complexes with other compounds. For example, the inventors have found the association constant of methane is three times higher for dimethylcucurbit[1,4]uril than for decamethylcucurbit[5]uril, and the association constant of dioxane in unsubstituted cucurbit[6]uril is two times higher than in tetramethylcucurbit[2,4]uril. To prepare a cucurbituril having the desired solubility together with the desired complexing properties for a particular application, it may be necessary to prepare a cucurbituril having particular groups at R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> at particular relative positions in the cucurbituril.

Further, for some applications, it is desirable to use variably substituted cucurbit[4 to 12]urils where only one or a few of the R<sup>1</sup> or R<sup>2</sup> groups in the cucurbituril is other than H, so that the cucurbituril has a similar ability to form complexes as an unsubstituted cucurbituril of the same degree of polymerisation but has a particular number and location of substituents that can react with other compounds, for example, to bind the cucurbituril to a solid support or to bind the cucurbituril to another cucurbituril.

The methods for preparing cucurbit[4 to 12]urils described in WO 00/68232 can be used to prepare certain variably substituted cucurbit[4 to 12]urils. However, when variably substituted cucurbit[4 to 12]urils are prepared by the methods described in WO 00/68232, a large number of different substituted cucurbiturils may be produced resulting in low yields of the desired variably

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substituted cucurbituril. For some applications, the desired variably substituted cucurbituril may need to be separated from the mixture of cucurbiturils produced, prior to the use of the variably substituted cucurbituril.

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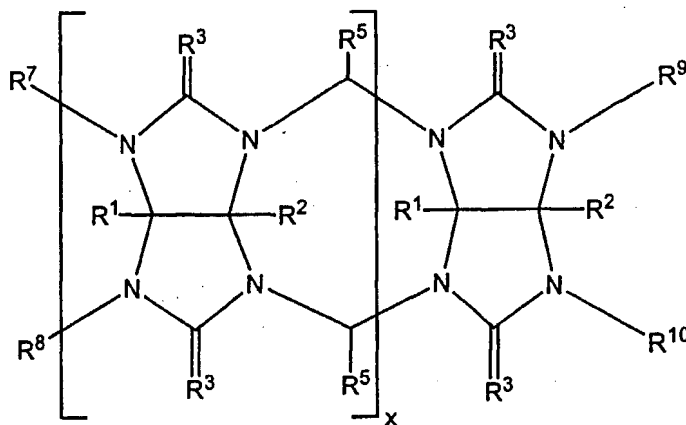
The inventors have therefore found that it would be advantageous to provide a method for preparing cucurbit[4 to 12]urils which allows a greater degree of control over the relative position of particular groups at R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> in the cucurbituril compared to prior art methods for preparing cucurbiturils. The inventors have in addition found such a method.

In one aspect, the present invention provides a method for preparing a cucurbit[n]uril, the method comprising the steps of:

15

(a) mixing

(1) a compound of the formula (1)



(1)

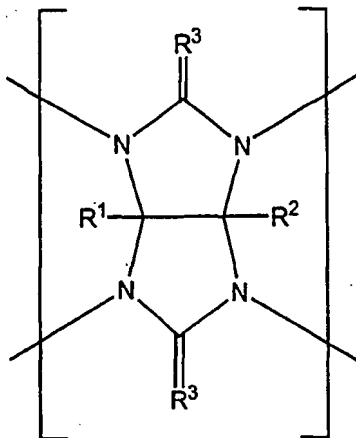
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wherein:

for each unit of the formula (A)



(A)

- 5 in the compound,  
 $R^1$  and  $R^2$  may be the same or different and are each a  
 univalent radical, or  
 $R^1$ ,  $R^2$  and the carbon atoms to which they are bound  
 together form an optionally substituted cyclic group, or  
 10  $R^1$  of one unit of the formula (A) and  $R^2$  of an adjacent  
 unit of the formula (A) together form a bond or a divalent  
 radical,  
 and  
 each  $R^3$  is independently selected from the group consisting  
 15 of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, wherein Z is an  
 electron withdrawing group such as -NO<sub>2</sub>, -CO<sub>2</sub>R, -COR, -CN  
 or -CX<sub>3</sub>, X is halo, and R is H, an optionally substituted  
 straight chain, branched or cyclic, saturated or  
 unsaturated hydrocarbon radical, or an optionally  
 20 substituted heterocyclyl radical;

each  $R^5$  is independently selected from the group consisting  
 of H, alkyl and aryl;

- 25  $R^7$  and  $R^8$  may be the same or different and are  
 independently selected from the group consisting of H and  
 -CHR<sup>5</sup>OR<sup>5</sup>, or  $R^7$  and  $R^8$  together form the group -CHR<sup>5</sup>-O-CHR<sup>5</sup>-

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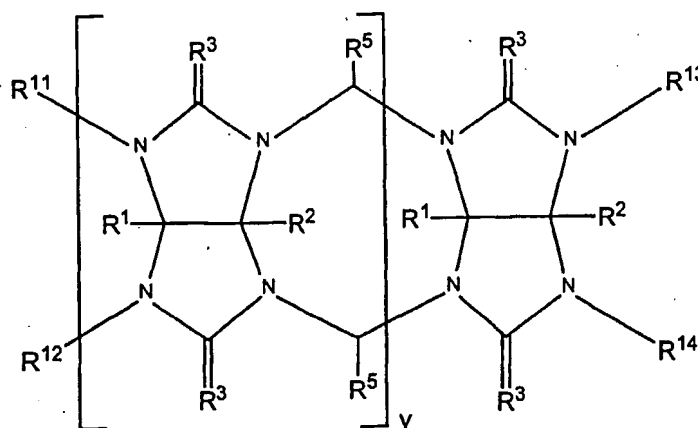
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, where each  $R^5$  is independently selected and is as defined above;

$R^9$  and  $R^{10}$  may be the same or different and are  
 5 independently selected from the group consisting of H and  $-\text{CHR}^5\text{OR}^5$ , or  $R^9$  and  $R^{10}$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$ , where each  $R^5$  is independently selected and is as defined as above; and

10  $x$  is an integer from 1 to 10;

(2) one or more compounds of the formula (2)



(2)

15

wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are as defined above for formula (1);

$R^{11}$  and  $R^{12}$  may be the same or different and are  
 20 independently selected from the group consisting of H and  $-\text{CHR}^5\text{OR}^5$ , or  $R^{11}$  and  $R^{12}$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$ , where each  $R^5$  is independently selected and is as defined above;

25  $R^{13}$  and  $R^{14}$  may be the same or different and are independently selected from the group consisting of H and  $-\text{CHR}^5\text{OR}^5$ , or  $R^{13}$  and  $R^{14}$  together form the group  $-\text{CHR}^5-\text{O}-$



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CHR<sup>5</sup>-, where each R<sup>5</sup> is independently selected and is as defined as above; and

y is 0 or an integer from 1 to 9 and x + y = 10 or less;  
5 and

(3) an acid;

to form a mixture;  
10 and

(b) exposing the mixture to conditions effective for the compound of the formula (1) and the one or more compounds of the formula (2) to form a cucurbit[n]uril.

15 In another aspect, the present invention provides a cucurbit[n]uril prepared by the method of the present invention.

As will be apparent to a person skilled in the art, R<sup>1</sup> and  
20 R<sup>2</sup> may be selected from a very broad range of substituents. The present invention is not limited to methods where R<sup>1</sup> and R<sup>2</sup> are particular groups.

When R<sup>1</sup> and R<sup>2</sup> are univalent radicals, R<sup>1</sup> and R<sup>2</sup> are  
25 typically independently selected from the group consisting of -R, -OR, -NR<sub>2</sub> where each R is independently selected, -NO<sub>2</sub>, -CN, -X,

30 -COR, -COX, -COOR,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{R}_2 \end{array}$  where each R is independently

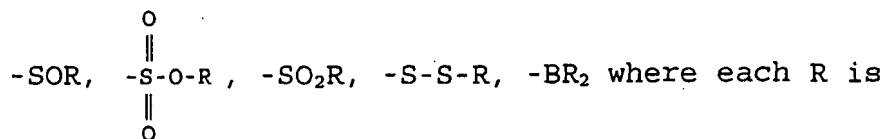
selected,  $\begin{array}{c} \text{NR} \\ \parallel \\ -\text{C}-\text{R} \end{array}$  where each R is independently selected,

35 -SeR, -SiR<sub>3</sub> where each R is independently selected, -SR,

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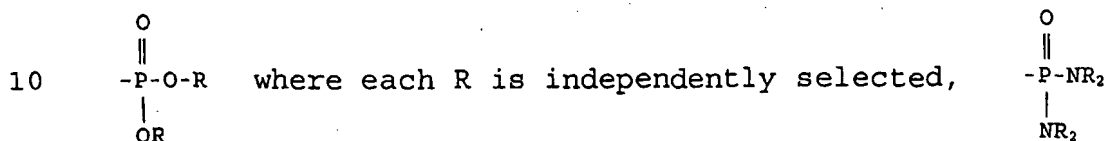
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independently selected,  $-\text{PR}_2$  where each R is independently selected,



10

where each R is independently selected,  $-\text{P}^+\text{R}_2$  where each R is independently selected and a metal or metal complex,

15

wherein R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and X is halo. In some embodiments, R is H, an optionally substituted  $\text{C}_{1-10}$  alkyl, an optionally substituted  $\text{C}_{2-10}$  alkenyl, or an optionally substituted  $\text{C}_{5-10}$  aryl.

20

The method of the present invention may produce a mixture of two or more different cucurbiturils. In accordance with the present invention, at least one of the cucurbiturils is formed from at least one compound of formula (1) and at least one of each of the compounds of formula (2). In some embodiments, at least some of the cucurbit[n]urils produced by the method of the present invention are formed from one compound of formula (1) and one of each of the compounds of formula (2). In some embodiments, at least some of the cucurbit[n]urils produced by the method of the present invention are formed from more than one compound of formula (1) and one of each of the compounds of formula (2), or from one compound of formula (1) and more than one of each of the compounds of

30

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formula (2).

Typically at least one of the one or more compounds of the formula (2) is different to the compound of the formula (1).

Typically  $R^7=R^8$ ,  $R^9=R^{10}$ ,  $R^{11}=R^{12}$  and  $R^{13}=R^{14}$ .

Typically step (a) comprises adding the compound of the formula (1) to the one or more compounds of the formula (2) and mixing, and then mixing the compounds with the acid. However, in some embodiments of the invention, the compound of the formula (1) is mixed with the acid, and the resultant mixture then added to the one or more compounds of the formula (2). Alternatively, in some embodiments of the invention, one or more of the compounds of the formula (2) is mixed with the acid, and the compound of the formula (1) and the remaining compounds of the formula (2), if any, are then added and mixed.

Typically step (b) comprises heating the mixture to a temperature of from 20°C to 120°C for a period of time sufficient for the compound of formula (1) and the one or more compounds of formula (2) to form a cucurbit[n]uril.

In some embodiments, step (b) further comprises incorporating into the mixture one or more compounds that can form bridges of the formula  $-CHR^5-$  between compounds of formula (1) and (2). As will be apparent to a person skilled in the art, the compound that can form bridges of the formula  $-CHR^5-$ , forms these bridges by reaction with, or replacement of, the groups  $R^7$  to  $R^{14}$  to form bridges of the formula  $-CHR^5-$  bound to the nitrogen atoms to which  $R^7$  to  $R^{14}$  were bound. Such a compound can be incorporated into the mixture by adding the compound to the mixture. Alternatively, the compound can be mixed with the compound of formula (1), the one or more compounds of formula (2)

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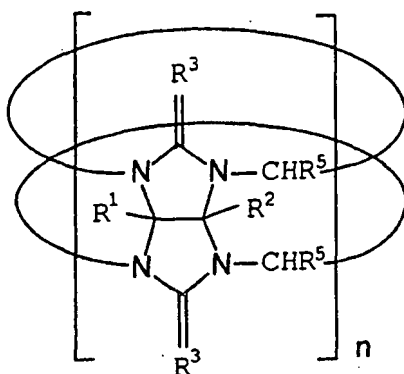
and/or the acid, prior to all these components being mixed together to form the mixture.

As will be apparent to a person skilled in the art, in some embodiments of the invention, it is not necessary to include a compound that can form bridges of the formula -CHR<sup>5</sup>- between compounds of formula (1) and (2) in the mixture in order to form a cucurbituril in step (b) of the method of the present invention. For example, if all the groups R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> in the compounds of formula (1) and (2) in the mixture are other than H, then the compounds of formula (1) and (2) can react to form a cucurbit[n]uril without the presence of such a compound.

However, if all of the groups R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> are H then such a compound must be included in the mixture in order for the compounds of formula (1) and (2) to form a cucurbit[n]uril.

Typically, if the molar ratio of the groups R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> in the compounds of formula (1) and (2) in the mixture which are H to those which are not H is greater than 1, then a compound that can form bridges of the formula -CHR<sup>5</sup>- between compounds of formula (1) and (2) is included in the mixture.

In another aspect, the present invention provides a cucurbit[n]uril of the formula:



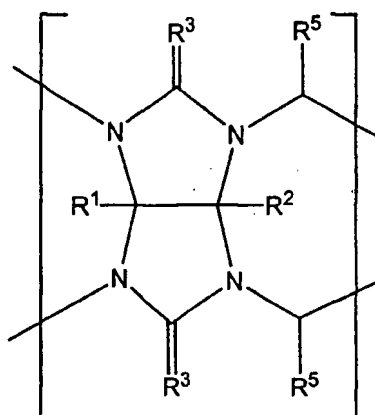
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wherein:

for each unit of the formula (B):



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(B)

in the cucurbit[n]uril,

10  $R^1$  and  $R^2$  may be the same or different and are each a univalent radical, or  $R^1$ ,  $R^2$  and the carbon atoms to which they are bound together form an optionally substituted cyclic group, or  $R^1$  of one unit of the formula (B) and  $R^2$  of an adjacent unit of the formula (B) together form a bond or a divalent radical,

15 each  $R^3$  is independently selected from the group consisting of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, wherein Z is an electron withdrawing group, X is halo and R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and  
20 each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;  
and n is an integer from 4 to 12,

25

and wherein at least one  $R^3$  in the cucurbit[n]uril is =CXZ, =CRZ or =CZ<sub>2</sub>.

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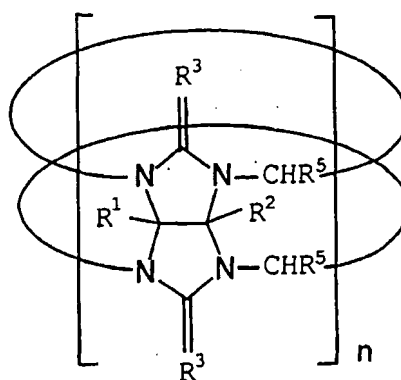
# DEFINITIONS

Having regard to the cucurbiturils described in WO 00/68232 and US patent no. 6,365,734 and the inventors' further work, the class of cucurbiturils is broader than that described in either of WO 00/68232 or US patent no. 6,365,734.

As used herein, the term "cucurbituril" refers to a compound of the formula (C):

15

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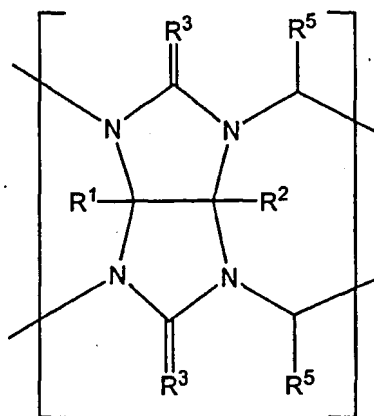


(C)

wherein:

for each unit of the formula (B):

25



(B)

in the compound,

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$R^1$  and  $R^2$  may be the same or different and are each a univalent radical, or  
 $R^1$ ,  $R^2$  and the carbon atoms to which they are bound together form an optionally substituted cyclic group, or  
 5  $R^1$  of one unit of the formula (B) and  $R^2$  of an adjacent unit of the formula (B) together form a bond or a divalent radical,  
 each  $R^3$  is independently selected from the group consisting of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, wherein Z is an  
 10 electron withdrawing group such as -NO<sub>2</sub>, -CO<sub>2</sub>R, -COR, -CN or -CX<sub>3</sub>, X is halo and R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and  
 15 each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;

and n is the degree of polymerisation, that is, the number of units of the formula (B) in the compound.

20 When  $R^1$  and  $R^2$  are univalent radicals,  $R^1$  and  $R^2$  are typically independently selected from the group consisting of -R, -OR, -NR<sub>2</sub> where each R is independently selected, -NO<sub>2</sub>, -CN, -X,

25 -COR, -COX, -COOR,  $\overset{\text{O}}{\parallel}$ -CR<sub>2</sub> where each R is independently

30 selected,  $\overset{\text{NR}}{\parallel}$ -C-R where each R is independently selected,

-SeR, -SiR<sub>3</sub> where each R is independently selected, -SR,

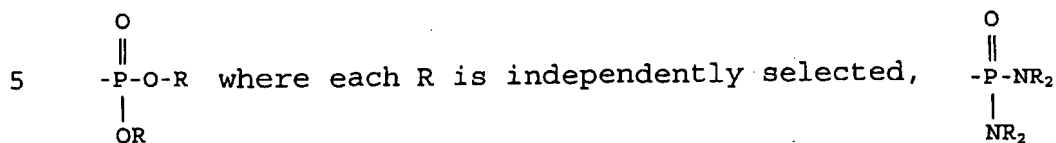
35 -SOR,  $\overset{\text{O}}{\parallel}$ -S-O-R, -SO<sub>2</sub>R, -S-S-R, -BR<sub>2</sub> where each R is

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independently selected,  $-PR_2$  where each R is independently selected,



where each R is independently selected,  $-P^*R_2$  where each R is independently selected and a metal or metal complex,

10

wherein R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and X is halo.

15

To differentiate various cucurbiturils, the inventors have adopted the term "cucurbit[n]uril", where n is the degree of polymerisation of the cucurbituril, that is, the number of units of the formula (B) in the macrocyclic ring of the cucurbituril. For example, a cyclic oligomer comprising eight units of the formula (B) joined together would be denoted as cucurbit[8]uril.

The present invention relates to cucurbit[n]urils where n is an integer from 4 to 12. Unless otherwise specified, the terms "cucurbituril" and "cucurbit[n]uril" as used herein refer to a cucurbit[n]uril where n is an integer from 4 to 12.

As used herein, the terms "unsubstituted cucurbituril" and "unsubstituted cucurbit[n]uril" refer to a cucurbituril in which  $R^3$  is =O, and  $R^1$ ,  $R^2$  and  $R^5$  are H, in all the units of formula (B) in the cucurbituril.

As used herein, the terms "variably substituted cucurbituril" and "variably substituted cucurbit[n]uril"



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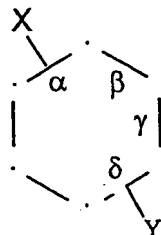
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refer to a cucurbituril in which the units of the formula (B) making up the cucurbituril are not all identical.

A variably substituted cucurbit[n]uril may consist of some unsubstituted units of the formula (B) where  $R^3$  is =O and  $R^1$ ,  $R^2$  and  $R^5$  are H, and some substituted units of the formula (B) where  $R^3$  is other than =O and/or one or more of  $R^1$ ,  $R^2$  and  $R^5$  is other than H. To differentiate such compounds, the term "cucurbit[s,u]uril" is used, where s equals the number of substituted units of the formula (B) and u equals the number of unsubstituted units of the formula (B), and s plus u equals n.

To indicate the relative location of the substituted units of the formula (B) in a variably substituted cucurbit[n]uril, a Greek letter is used with  $\alpha$  being assigned to a substituted unit of the formula (B) given first priority and all other units of the formula (B) in the macrocyclic ring of the cucurbit[n]uril are assigned a Greek letter in alphabetical order. For example, a cucurbit[6]uril having two units of the formula (B) substituted by X and Y respectively, where the substituted units of the formula (B) are located at opposite sides of the cucurbituril, would be identified by the name  $\alpha$ X, $\delta$ Y-cucurbit[2,4]uril. The following representation illustrates such a cucurbit[6]uril when viewed towards one of the portals of the cucurbituril:

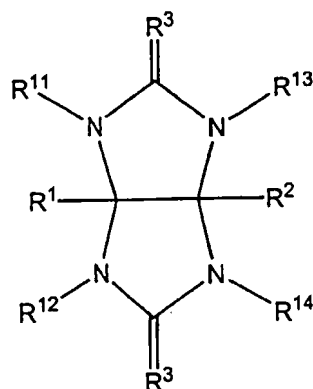


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As used herein, the term "glycoluril analogue" refers to a compound of the formula (5):



(5)

5

wherein

$R^1$  and  $R^2$  may be the same or different and are each a univalent radical, or

10  $R^1$ ,  $R^2$  and the carbon atoms to which they are bound together form an optionally substituted cyclic group, and  $R^3$  and  $R^{11}$  to  $R^{14}$  are as defined above for formula (2).

Typically, when  $R^1$  and  $R^2$  are univalent radicals,  $R^1$  and  $R^2$  are independently selected from the group consisting of -  
 15  $R$ ,  $-OR$ ,  $-SR$ ,  $-NR_2$  where each  $R$  is independently selected,  $-NO_2$ ,  $-CN$ ,  $-X$ ,

20

$-COR$ ,  $-COX$ ,  $-COOR$ ,  $-CR_2$  where each  $R$  is independently

selected,  $-C(=NR)-R$  where each  $R$  is independently selected,

$-SeR$ ,  $-SiR_3$  where each  $R$  is independently selected,  $-SR$ ,

25

$-SOR$ ,  $-S(=O)_2-O-R$ ,  $-SO_2R$ ,  $-S-S-R$ ,  $-BR_2$  where each  $R$  is

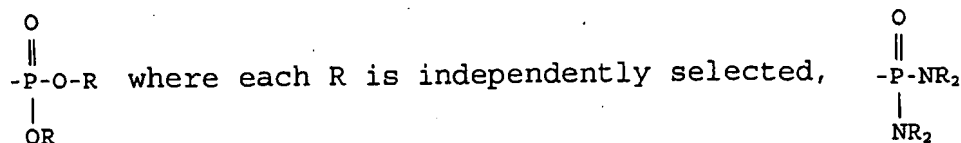
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independently selected,  $-PR_2$  where each R is independently selected,

5



- 10 where each R is independently selected,  $-P^+R_2$  where R is independently selected and a metal or metal complex, wherein R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocycl
- 15 radical, and X is halo.

#### DETAILED DESCRIPTION OF PREFERRED EMDODIMENTS

Various cucurbit[4 to 12]urils of formula (C) as defined  
 20 above are novel. In particular, cucurbit[4 to 12]urils of formula (C) where:

1. one or more of the  $R^3$  groups in the cucurbituril is other than =O, =S or =NH; or
- 25 2. each of the  $R^3$  groups in the cucurbituril is =O, =S or =NH, at least one of the  $R^3$  groups is =S or =NH, and not all the  $R^1$ ,  $R^2$ ,  $R^3$  or  $R^5$  groups in the cucurbituril are the same; or
3. each of the  $R^3$  groups in the cucurbituril is =O, =S  
 30 or =NH, one or more of the  $R^5$  groups in the cucurbituril is other than H, and not all of the  $R^1$ ,  $R^2$ ,  $R^3$  or  $R^5$  groups in the cucurbituril are the same;

are not disclosed in the prior art.

35

The method of the present invention involves preparing cucurbiturils using at least one compound comprising two

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or more units of the formula (A) joined by bridges of the formula  $-\text{CHR}^5-$  (the compound of formula (1)). As this compound comprises two or more units of the formula (A), the particular  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{R}^5$  groups in the compound have a fixed position relative to each other which is retained in the cucurbiturils prepared from that compound. Thus the method of the present invention when used to prepare variably substituted cucurbiturils, results in the production of a lesser variety of different variably substituted cucurbit[n]urils than the prior art methods which comprise reacting glycoluril analogues to form cucurbiturils. Accordingly, the method of the present invention allows a greater degree of control over the types of substituted cucurbiturils produced than the prior art methods for preparing cucurbiturils.

As will be apparent to a person skilled in the art, if the groups  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$  and  $\text{R}^{14}$  in the compounds of formula (1) and (2) are other than hydrogen, the compounds of formula (1) and (2) can react with each other to form a cucurbituril in step (b) of the method. However, if all of these groups are H, or if, in the compounds of formula (1) and (2) that are to form the cucurbituril, the total number of these groups which are H is greater than the total number which are not H, then a compound that can form bridges of the formula  $-\text{CHR}^5-$  between compounds of formula (1) and (2) must be included in the mixture in order for the compound of formula (1) and the one or more compounds of formula (2) to form a cucurbituril in step (b) of the method.

In formulas (1), (2), (3), (4) and (5), when  $\text{R}^1$  and  $\text{R}^2$  are univalent radicals,  $\text{R}^1$  and  $\text{R}^2$  may for example be selected from H, an optionally substituted alkyl (e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, etc), optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted

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heterocyclyl or optionally substituted aryl (e.g. phenyl, naphthyl, pyridyl, furanyl or thiophenyl), -OR, -SR or -NR<sub>2</sub>.

- 5 In some embodiments, when R<sup>1</sup> and R<sup>2</sup> are univalent radicals, R<sup>1</sup> and R<sup>2</sup> include less than 30 carbon atoms. R<sup>1</sup> and R<sup>2</sup> may for example be selected from the group consisting of alkyl groups of 1 to 30 carbon atoms, alkenyl groups of 1 to 30 carbon atoms, cyclic hydrocarbon groups of 5 to 30 carbon atoms, cyclic groups of 4 to 30 carbon atoms with one or  
10 more heteroatoms such as O, N or S, aryl groups of 6 to 30 carbon atoms, and aryl groups of 5 to 30 carbon atoms with one or more hetero atoms such as O, N or S.
- 15 R<sup>1</sup> and R<sup>2</sup> may for example be an alkoxy group such as methoxy, ethoxy, propyloxy etc. R<sup>1</sup> and R<sup>2</sup> may also be a hydroxy, halo, cyano, nitro, amino, alkylamino or alkylthio radical.
- 20 Examples of optionally substituted cyclic groups formed by R<sup>1</sup>, R<sup>2</sup> and the carbon atoms to which they are bound, include optionally substituted saturated or unsaturated cyclic hydrocarbon groups of 5 to 30 carbon atoms, and optionally substituted saturated or unsaturated cyclic  
25 groups of 3 to 30, typically 4 to 30, carbon atoms with one or more heteroatoms such as O, N or S.

When R<sup>1</sup> and R<sup>2</sup> of adjacent units of the formula (A) in the compound of formula (1) or formula (2), or adjacent units  
30 of the formula (B) in a cucurbituril, together form a divalent radical, the divalent radical may for example, be a divalent optionally substituted straight chain or branched, saturated or unsaturated hydrocarbon radical comprising 1 or more carbon atoms. The divalent radical  
35 may consist of or contain one or more heteroatoms such as O, N or S.

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When R is an optionally substituted hydrocarbon radical or an optionally substituted heterocyclyl radical, the hydrocarbon radical or the heterocyclyl radical may be substituted by one or more substituents. Similarly, when  
5 R<sup>1</sup>, R<sup>2</sup> and the carbon atoms to which they are bound together form an optionally substituted cyclic group, the cyclic group may be substituted by one or more substituents. The optional substituents can be any group and may for example be an optionally substituted alkyl, an  
10 optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted heterocyclyl, an optionally substituted aryl, halo (e.g. F, Cl, Br or I), hydroxyl, alkoxyl, carbonyl, acyl halide, nitro, carboxylic acid, carboxylic acid ester, amino, imino,  
15 cyano, isocyanate, thiol, thiol-ester, thio-amide, thio-urea, sulfone, sulfide, sulfoxide or sulfonic acid group or a metal or metal complex. The optional substituent may also be a borane, a phosphorous containing group such as a phosphine, alkyl phosphine, phosphate or phosphoramidate, a  
20 silicon containing group or a selenium containing group.

Typically Z is selected from the group consisting of -NO<sub>2</sub>, -CO<sub>2</sub>R, -COR, -CN and -CX<sub>3</sub>, where X is halo (e.g. F, Cl, Br or I) and R is H, alkyl (for example, methyl, ethyl,  
25 propyl, etc), alkenyl, alkynyl, aryl, heteroaryl or saturated or unsaturated heterocyclyl.

The compound that can form bridges of the formula -CHR<sup>5</sup>- between compounds of formula (1) and (2) is typically  
30 selected from a compound of the formula R<sup>5</sup>COR<sup>5</sup> or a compound of the formula R<sup>5</sup>OC(R<sup>5</sup>)<sub>2</sub>OR<sup>5</sup>, where R<sup>5</sup> is as defined above and each R<sup>5</sup> group is independently selected, trioxane, optionally substituted 3,4-dihydropyran or optionally substituted 2,3-dihydrofuran. The optionally  
35 substituted 3,4-dihydropyran or optionally substituted 2,3-dihydrofuran may be substituted by groups such as

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alkyl, alkenyl, alkynyl, aryl or halo. The compound of the formula  $R^5COR^5$  may for example be formaldehyde.

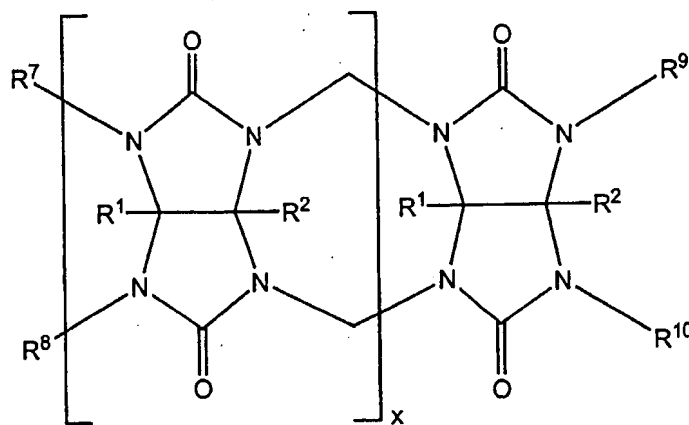
$R^5$  is H, alkyl or aryl. When  $R^5$  is alkyl,  $R^5$  is typically a C<sub>1-5</sub> alkyl, such as methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, tert-butyl etc. When  $R^5$  is aryl,  $R^5$  may for example be phenyl.

The majority of cucurbit[4 to 12]urils prepared to date are cucurbit[4 to 12]urils wherein  $R^3$  is =O and  $R^5$  is H in all units of the formula (B) making up the cucurbituril.

In one embodiment, the present invention provides a method for preparing such a cucurbit[4 to 12]uril, the method comprising the steps of:

(a) mixing

(1) a compound of the formula (3)



(3)

20

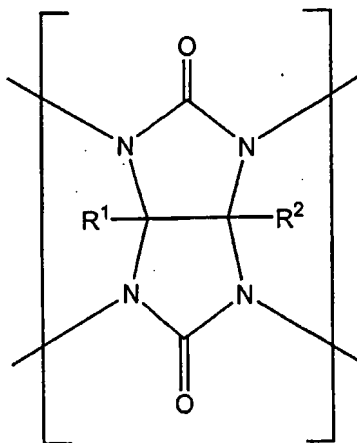
wherein:

for each unit of the formula (D):

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(D)

in the compound,

$R^1$  and  $R^2$  may be the same or different and are each a  
 5 univalent radical, or  
 $R^1$ ,  $R^2$  and the carbon atoms to which they are bound  
 together form an optionally substituted cyclic group, or  
 $R^1$  of one unit of the formula (D) and  $R^2$  of an adjacent  
 unit of the formula (D) together form a bond or a divalent  
 10 radical;

$R^7$  and  $R^8$  may be the same or different and are  
 independently selected from the group consisting of H and  
 $-\text{CH}_2\text{OH}$ , or  $R^7$  and  $R^8$  together form the group  $-\text{CH}_2-\text{O}-\text{CH}_2-$ ;

15  $R^9$  and  $R^{10}$  may be the same or different and are  
 independently selected from the group consisting of H and  
 $-\text{CH}_2-\text{OH}$ , or  $R^9$  and  $R^{10}$  together form the group  $-\text{CH}_2-\text{O}-\text{CH}_2-$ ;

20 and  $x$  is an integer from 1 to 10;

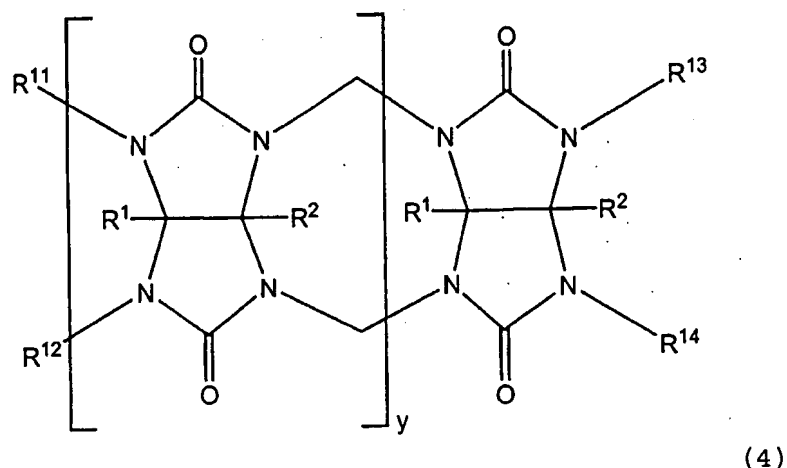
(2) one or more compounds of the formula (4)



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wherein:

5  $R^1$  and  $R^2$  are as defined above for formula (3);

$R^{11}$  and  $R^{12}$  may be the same or different and are independently selected from the group consisting of H and  $-CH_2OH$ , or  $R^{11}$  and  $R^{12}$  together form the group  $-CH_2-O-CH_2-$ ;

10

$R^{13}$  and  $R^{14}$  may be the same or different and are independently selected from the group consisting of H and  $-CH_2OH$ , or  $R^{13}$  and  $R^{14}$  together form the group  $-CH_2-O-CH_2-$ ;

15 and  $y$  is 0 or an integer from 1 to 9 and  $x + y = 10$  or less;  
and

(3) an acid;

to form a mixture; and

20 (b) exposing the mixture to conditions effective for the compound of the formula (1) and the one or more compounds of the formula (2) to form a cucurbit[n]uril.

In such an embodiment of the invention, if a compound that  
25 can form bridges of the formula  $-CHR^5-$  between the compounds of formula (4) and (5) is used, the compound is selected from formaldehyde, paraformaldehyde, trioxane, 2,3-dihydropyran or 2,3-dihydrofuran.

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Typically the mixture formed in step (a) of the method of the present invention further comprises a templating compound. As used herein, the term "templating compound" refers to a compound that affects the relative amount of cucurbit[n]urils of differing degrees of polymerisation prepared by the method of the present invention. For example a templating compound when added to the mixture, may alter the ratio of, say, cucurbit[5]uril to cucurbit[6]uril, when that ratio is compared with that ratio of cucurbit[5]uril to cucurbit[6]uril that is produced using mixtures not containing a templating compound or containing a different templating compound, but otherwise reacted under identical conditions.

Typically, the templating compound is a salt. However, it has been found that many other compounds can also act as a templating compound.

Any compound that can alter the ratio of cucurbiturils of different degrees of polymerisation prepared by the method of the present invention can be used as the templating compound. The templating compound may be an organic compound, a salt of an organic compound, or an inorganic compound. Suitable compounds that may be used as a templating compound include ammonium chloride, lithium chloride, sodium chloride, potassium chloride, rubidium chloride, caesium chloride, ammonium bromide, lithium bromide, sodium bromide, potassium bromide, rubidium bromide, caesium bromide, lithium iodide, sodium iodide, potassium iodide, rubidium iodide, caesium iodide, potassium sulfate, lithium sulfate, tetrabutylammonium chloride, tetraethylammonium chloride, o-carborane, thioacetamide, N-(1-naphthyl) ethylenediamine, 2,2'-biquinoline, p-bromoaniline, taurine, blue tetrazolium, 2-amino-3-methyl benzoic acid, indol-3-aldehyde, cysteine, 4-acetamidoaniline, p-aminophenol, acetamide, 4-

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aminoacetophenone, 4-dimethylaminobezaldehyde, 2-aminobenzimidazol, bis-(4,4'-bipyridyl)- $\alpha,\alpha'$ -xylene, red phosphorus, and lithium p-toluenesulfonate. The present inventors believe that a large number of other compounds  
5 could be suitable for use as templating compounds and therefore the above list should not be considered to be exhaustive. The anions of the acid may also be considered to be a templating compound.

10 The templating compounds may be added singly to the reaction mixture, or two or more templating compounds may be added to the reaction mixture.

If a salt is used as the templating compound, the salt is  
15 preferably a metal halide, ammonium halide, metal sulphate or metal tosylate. It is preferred that the anion of the salt corresponds to the anion of the acid used. For example, where the acid used is hydrochloric acid, a metal chloride or ammonium chloride is a preferred salt.

20 Similarly, iodide-containing salts are preferably used when the acid is hydriodic acid, and bromide-containing salts are preferably when the acid is hydrobromic acid.

The acid is preferably a strong mineral acid or a strong  
25 organic acid. In principle, any acid can be used. The acid acts to catalyse the reactions taking place.

Preferred acids include sulfuric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, deuterated sulfuric  
30 acid, phosphoric acid, p-toluenesulfonic acid, and methane sulphononic acid. It will be appreciated that this list is not exhaustive and that any acid that can catalyse the reaction may be used in the method of the present invention.

35 It is preferred that the acid has a concentration of at least 5M. It is also preferred that the concentration of

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the acid in the mixture comprising the compound of formula (1), the one or more compounds of formula (2) and the acid, is at least 5M.

5 Typically the mixture is not an anhydrous mixture.

The mixture may further comprise a solvent. The solvent may for example be selected from trifluoroacetic acid, methanesulfonic acid, 1,1,1-trifluoroethanol or an ionic  
10 liquid.

Step (b) of the method of the present invention typically comprises heating the mixture to a temperature of from 20°C to 120°C for a period of time sufficient for the compound  
15 of the formula (1) and the one or more compounds of the formula (2) to form a cucurbit[n]uril. Typically the temperature is 60°C to 110°C, most preferably from 80°C to 110°C. It is preferred that boiling of the mixture is avoided. Heating under reflux is not required but may be  
20 used. It has been found that the mixture should be generally heated to a temperature of 60°C and above to produce cucurbit[n]urils, with increased yields being obtained at temperatures in the range of 80°C to 100°C.

25 Preparation of Compounds of Formula (1) and (2)

(a) *Substituted glycolurils and glycoluril analogues*

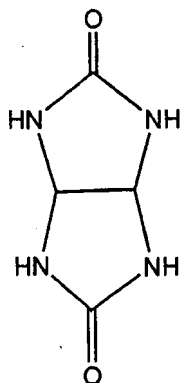
Formula (2) encompasses glycoluril analogues of the  
30 formula (5) as defined above.

Formula (5) encompasses glycoluril of the formula:

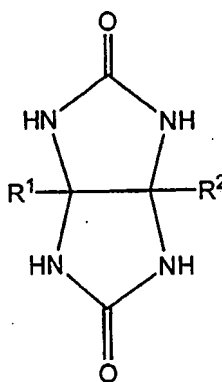
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Formula (5) also encompasses substituted glycolurils of the formula:



5

There are a large number of substituted glycolurils known in the literature. Particular reference is made to the review article by Harro Petersen in *Synthesis*, 1973, 249-293, incorporated herein by reference. That review  
10 article contains a list of about 30 substituted glycolurils. The literature since that article has disclosed several other examples of substituted glycolurils and it is believed that essentially any  $\alpha$ - or  $\beta$ -diketone could be used to make a substituted or  
15 unsubstituted glycoluril.

Further substituted glycolurils are disclosed in WO 00/68232.

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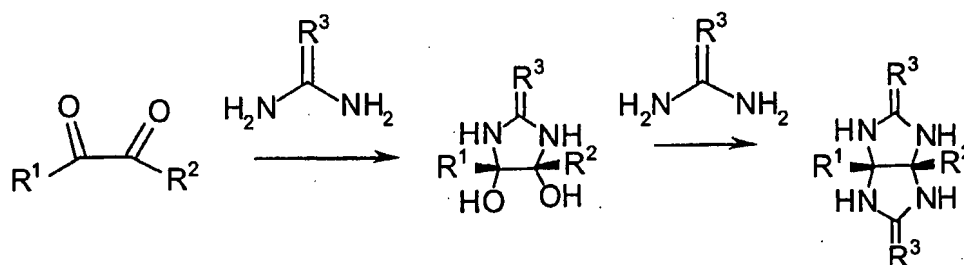
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Glycoluril analogues can be prepared by methods known in the art, for example as described in the review article by Harro Petersen in Synthesis, 1973, 249-293

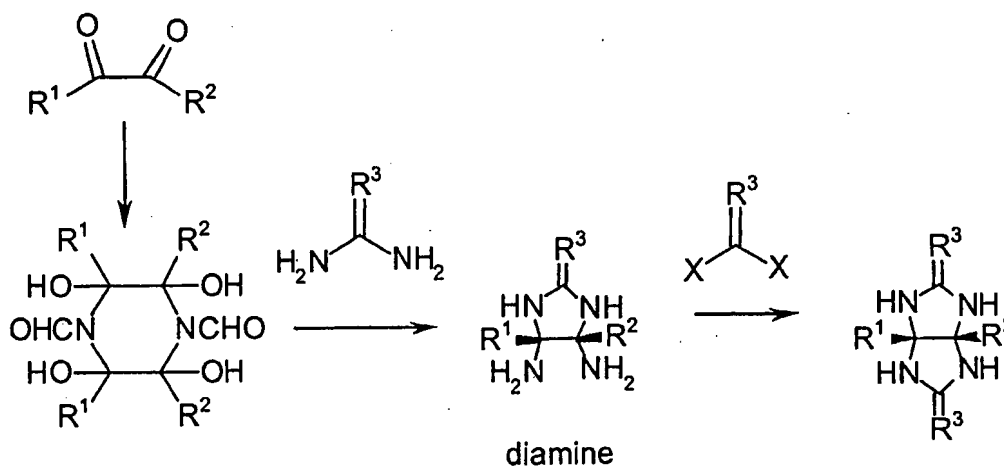
- 5 Glycoluril analogues can for example be prepared as described in the following reaction schemes:

Scheme 1

10



Scheme 2



- wherein each  $R^1$ ,  $R^2$  and  $R^3$  group is independently selected and is as defined above for formula (2), and X is a leaving group such as a halo or a thioether.

The reactions of Scheme 1 may be carried out under the following conditions:

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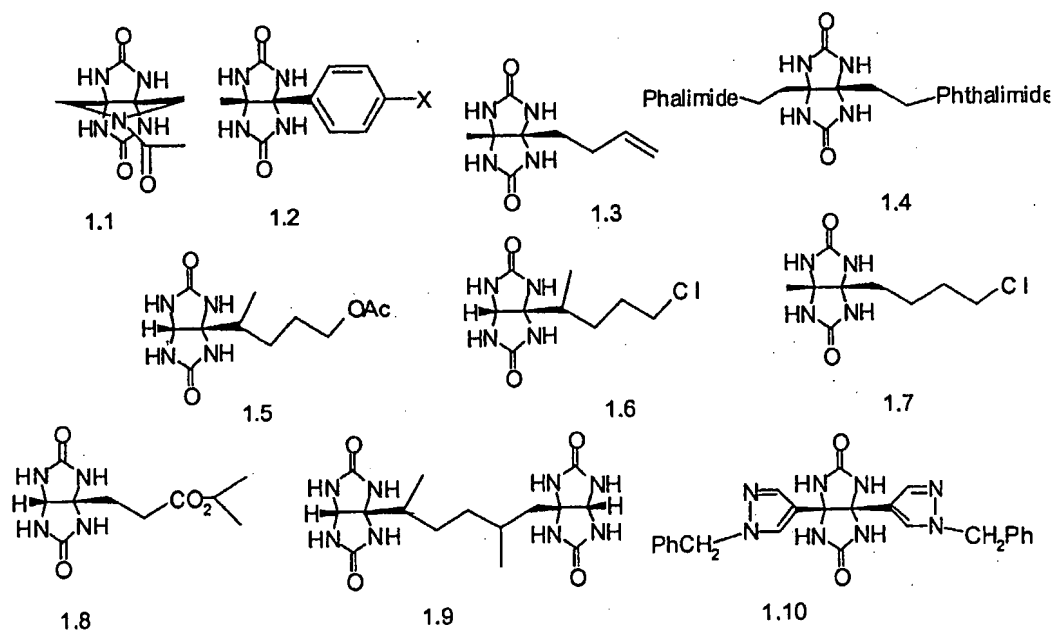
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- a) Reaction in water at room temperature for several days;
- b) Reaction in acidic water with or without a cosolvent;
- 5 c) Reaction in a hydrocarbon solvent in the presence of an acid catalyst while water of reaction is removed azeotropically;
- d) Reaction in a hydrocarbon solvent in the presence of a Lewis acid with or without removal of water
- 10 generated during reaction.

Scheme 1 can, for example, be used to prepare the following substituted glycolurils (in compound 1.2, X is halo). These compounds are new, and form a further aspect

15 of the present invention.



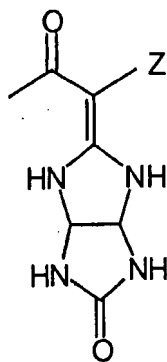
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In scheme 2, the reaction to form the diamine intermediate is carried out in acid water with or without a cosolvent. The reaction of the diamine intermediate to form the glycoluril analogue is carried out under basic conditions.

- 5 An example of the reaction of scheme 2 to form a glycoluril analogue where one  $R^3$  group is =NH and the other  $R^3$  is =O is described in I.J. Dagley and M. Kony, Heterocycles 1994, 38, 595.
- 10 Scheme 2 can for example, be used to prepare the glycoluril analogues 1.11 and 1.12.



1.11 Z = CN

15

1.12 Z = COCH<sub>3</sub>

(b) Compounds of formula (1) where  $R^7$  to  $R^{10}$  is not H and compounds of formula (2) where  $R^{11}$  to  $R^{14}$  is not H

- 20 Compounds of formula (2) in which  $R^{11}$  and  $R^{12}$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$  and  $R^{13}$  and  $R^{14}$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$ , can be prepared by mixing a compound of formula (2) in which  $R^{11}$  to  $R^{14}$  are H, with trioxane, a compound of the formula  $(R^5)_2\text{CO}$  or a compound of the
- 25 formula  $R^5\text{OC}(R^5)_2\text{OR}^5$ , where  $R^5$  is as defined above and each  $R^5$  is independently selected, and an acid, and heating the mixture to about 20°C to 60°C. Typically, when a strong mineral acid or strong organic acid is used the mixture heated to between 20°C to 40°C. However, if a weaker acid



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such as trifluoroacetic acid is used, the mixture can be heated to about 60°C.

Compounds of the formula (2) in which some or all of  $R^{11}$  to  $R^{14}$  are  $-\text{CHR}^5\text{OR}^5$  can be prepared by reacting a compound of formula (2) in which  $R^{11}$  to  $R^{14}$  are H with a compound of the formula  $\text{XHR}^5\text{COR}^5$ , where X is halo and each  $R^5$  is independently selected and is as defined above, under basic conditions. The reaction typically occurs at room temperature, but the reaction mixture can be heated to about 40°C.

The same methods can be used to prepare compounds of formula (1) in which  $R^7$  and  $R^8$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$  and  $R^9$  and  $R^{10}$  together form the group  $-\text{CHR}^5-\text{O}-\text{CHR}^5-$ , and compounds of formula (1) in which some or all of  $R^7$  to  $R^{10}$  are  $-\text{CHR}^5\text{OR}^5$ .

#### Example 1

To 3a-(4-(1-chlorobutane)-6a-methylglycoluril (compound 1.7) (1 g, 4.2 mmol) suspended in 7M hydrochloric acid (1.27 mL) was added 40% formaldehyde (15 mL) and the mixture stirred at room temperature for 18h. The resultant precipitated diether was collected by filtration washed with water and dried.

#### Example 2

To 3a-(p-iodophenyl)-6a-methylglycoluril (compound 1.2 where X=I) (1 g, 1.8 mmol) dissolved in concentrated sulfuric acid (7 mL) was added 40% formaldehyde (1.7 mL) at room temperature. After 20-30 min the mixture was poured into ice water and the precipitated diether was collected by filtration and dried at 80°C in vacuo, yield 80%.

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## Example 3

To 3a,6a-diphenylglycoluril (1 g, 1.8 mmol) dissolved in concentrated sulfuric acid (7 mL) was added 40% formaldehyde (0.7 mL) at room temperature. After 20-30 min the mixture was poured into ice water and the precipitated diether was collected by filtration and dried at 80°C in vacuo, yield 95%.

## Example 4

To 3a,6a-di(p-iodophenyl)glycoluril (1g, 1.8 mmol) dissolved in concentrated sulfuric acid (6 mL) was added 40% formaldehyde (0.54 mL) at room temperature. After 20-30 min the mixture was poured into ice water and the precipitated diether was collected by filtration and dried at 80°C in vacuo.

## Example 5

3a,6a-cyclopentanoglycoluril (1 g, 5.49 mmol) was added to a mixture of dimethylsulfoxide (1 mL), water (2 mL) and 40% formaldehyde (1.6 mL) at room temperature and the pH of the mixture adjusted to 9 with 1 M NaOH. After 12h the mixture was poured into methanol (15 mL) and the precipitated tetrol (compound 2.6) was collected by filtration and dried at 80°C in vacuo 82% yield.

## Example 6

To 3a-(4-but-2-ene)-6a-methylglycoluril (compound 1.3) (1 g, 0.48 mmol) dissolved in trifluoroacetic acid (2 mL) was added 40% formaldehyde (1.46 mL) and the mixture heated to 60°C for 12h. Evaporation of the solvent afforded the diether, yield 70%. At short reaction times of less than 1hr a mixture of alcohols and ethers is formed.

Diether analogues of glycoluril can also be prepared under anhydrous conditions, similar to the method of A. Wu, A. Chakraborty, D. Witt, J. Lagona, F. Damkai, M. A. Ofori,

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J. K. Chiles, J. C. Fettingner, and L. Isaacs J. *Org.Chem.* 2002, 67, 5817-5830, incorporated herein by reference.

(b) *Oligomers of formula (1) or (2)*

5  
Glycoluril analogues can be used to prepare oligomers of formula (1) and (2) comprising 2 to 11 units of formula (A) linked by bridges of the formula  $-\text{CHR}^5-$ . The oligomers can be prepared by mixing one or more glycoluril analogues  
10 with an acid, and if required a compound that can form bridges of the formula  $-\text{CHR}^5-$  between such compounds, and heating the mixture. The compound that can form bridges of the formula  $-\text{CHR}^5-$  may be trioxane, a compound of the formula  $\text{R}^5\text{COR}^5$  or a compound of the formula  $\text{R}^5\text{OC}(\text{R}^5)_2\text{OR}^5$ ,  
15 wherein  $\text{R}^5$  is as defined above and each  $\text{R}^5$  is independently selected.

The inventors have found that using suitable reaction temperatures and reaction times oligomers comprising 2 to  
20 11 units of the formula (A) linked by bridges of the formula  $-\text{CHR}^5-$  can be prepared without the oligomers reacting to form cucurbiturils. Typically the oligomers are prepared by heating the reaction mixture to a temperature below  $50^\circ\text{C}$  for a period of less than about 20  
25 hours.

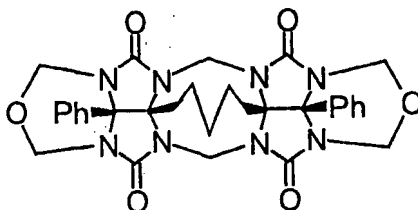
This process typically results in the production of a mixture of oligomers comprising different numbers of units of the formula (A). If desired, an oligomer having a  
30 particular length may be separated from the other oligomers in the mixture by crystallisation or chromatography. However, in many cases, an oligomer of one particular length is predominantly formed, and in such a case it may not be necessary to separate that oligomer  
35 from the other oligomers formed, prior to using the oligomer in the method of the present invention.

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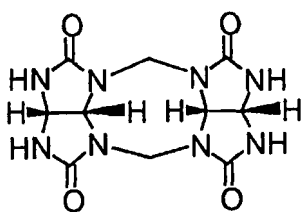
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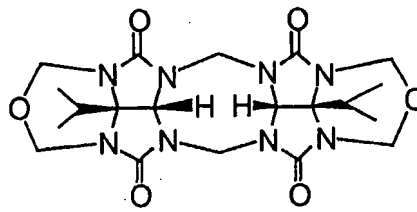
Certain compounds referred to the following examples are represented by the structures:



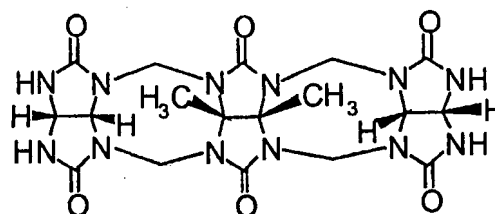
2.1 diether dimer



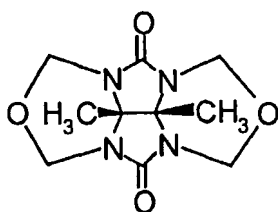
2.2 dimer



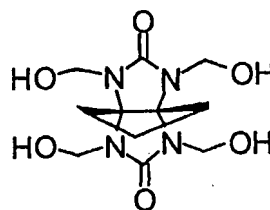
2.3 diether dimer



2.4 Trimer



2.5 diether



2.6 tetrol

#### Example 7

- 5 To 3a-isopropylglycoluril (1 g, 5.4 mmol) dissolved in trifluoroacetic acid (15 mL) was added 40% formaldehyde (1.62 mL) and the mixture heated at 50°C or reflux for 24h. The solvent was evaporated to give predominantly the diether dimer (compound 2.3) which was purified or used
- 10 crude.

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## Example 8

To alkyltethered bisglycoluril (compound 1.9) (500 g, 1.9 mmol) dissolved in trifluoroacetic acid (15 mL) was added 40% formaldehyde (0.855 mL) and the mixture heated at 50°C or reflux for 24h. The solvent was evaporated to give predominantly the dimer which was purified or used crude.

## Example 9

To 3a-(4-(1-chloro-4-methylbutane)glycoluril (compound 1.6) (1 g, 4.2 mmol) dissolved in trifluoroacetic acid (15 mL) was added 40% formaldehyde (1.26 mL) and the mixture heated at 50°C or reflux for 24h. The solvent was evaporated to give the dimer derivative as a diether.

## Example 10

The formaldehyde diether derivative of 3a-(4-(1-chloro-4-methylbutane)glycoluril (compound 1.6) (1 g, 2.9 mmol) and the unsubstituted glycoluril dimer (compound 2.2) (1.8 g, 5.8 mmol) were mixed together in concentrated HCl (5 mL) at room temperature. After 30 mins and up to 1 hr the homogeneous mixture was poured into MeOH (10 mL) and the precipitate collected and dried to give predominantly the pentamer.

## Example 11

The formaldehyde diether derivative of 3a,6a-diphenylglycoluril (2.9 g, 7.7 mmol), the unsubstituted glycoluril dimer (compound 2.2) (4.7 g, 15.4 mmol) and  $K_2CO_3$  (530 mg) were mixed together in methanesulfonic acid (40 mL) at room temperature, 20 min then 10min at 50°C. The homogeneous mixture was poured into MeOH (60 mL) and the precipitate collected and dried to give predominantly the pentamer.

## Example 12

The formaldehyde diether derivative (compound 2.5) of dimethylglycoluril (1 g, 5.9 mmol) and unsubstituted

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glycoluril dimer (compound 2.2) (0.91 g, 2.95 mmol) in conc. HCl (2 mL) were stirred together at room temperature for 30 min to 1 hr and the homogeneous mixture was poured into MeOH (10 mL) and the precipitate collected and dried to give predominantly the diether tetramer.

#### Example 13

The tetrol derivative (compound 2.6) of 3a,6a-cyclopentanoglycoluril (1 g, 3.3 mmol) was added to a solution of unsubstituted glycoluril (937 mg, 6.6 mmol) in conc. HCl (2 mL) and the mixture stirred at room temperature for 30 min. The homogeneous mixture was poured into MeOH (10 mL) and the precipitate collected and dried to give predominantly the trimer.

#### Example 14

A mixture of the diether (compound 2.5) of dimethylglycoluril (1 g, 3.9 mmol), glycoluril (1.1 g, 7.75 mmol) and LiCl (250 mg) were ground together to give a fine powder. To this mixture was added 8 M HCl (10 mL) and the mixture stirred for 1 hr at ambient temperature, after which time all the solid material had dissolved. The mixture was then heat at 50°C for 12 to 24 hr. After cooling the solvent was evacuated in vacuo. Recrystallisation from combinations of methanol and dilute acid solutions gave the trimer (compound 2.4) 1.2 g as a pure compound.

#### Synthesis of cucurbit[4 to 12]urils

#### Example 15

The unsubstituted glycoluril dimer (compound 2.2) (357 mg, 1.2 mmol) and the diether (compound 2.5) of dimethylglycoluril (148 mg, 0.58 mmol) were mixed and ground together as a fine powder and added to concentrated hydrochloric acid (14 mL). The mixture was stirred at room temperature for 1 hr to form the pentamer, then

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paraformaldehyde (35 mg) was added and the mixture heated to 100°C for 2-3 hr. Evaporation of the acid *in vacuo* gave dimethylcucurbit[1,4]uril as the major product.

5 Example 16

The unsubstituted glycoluril dimer (compound 2.2) (2.36 mg, 7.7 mmol) and the diether of dimethylglycoluril (compound 2.5) (1.96 mg, 7.7 mmol) and LiCl were mixed and ground together as a fine powder and added to concentrated  
10 hydrochloric acid (12 mL). The mixture was stirred at room temperature for 30 min. The mixture was heated to 100°C for 2-3 hr. Evaporation of the acid *in vacuo* gave  $\alpha,\delta$ -tetramethylcucurbit[2,4]uril as the major product, >80%. The product was purified on Dowex cation exchange  
15 resin eluting with a mixture of formic acid and 1M HCl.

Example 17

3a-isopropylglycoluril dimer diether (compound 2.3) (1 g, 2.5 mmol) and unsubstituted glycoluril (720 mg, 5.0 mmol)  
20 were mixed in 7M hydrochloric acid (12 mL). The mixture was stirred at room temperature for 1 hr. The mixture was heated to 100°C for 2-3 hr. Evaporation of the acid *in vacuo* gave the  $\alpha,\beta,\delta,\epsilon$ -tetraisopropylcucurbit[4,2]uril as the major product.

25

Example 18

The unsubstituted glycoluril dimer (compound 2.2) (183 mg, 0.6 mmol), the diether of butylimideglycoluril (210 g, 0.64 mmol) and *p*-toluenesulfonic acid (925 g) were ground  
30 together. The mixture was heated to 110°C for 2-3 hr. Methanol was added to the hot mixture and cooled. The precipitate was collected by filtration. Purification by chromatography gave the  $\alpha,\delta$ -dibutylimidecucurbit[2,4]uril as the major product.

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## Example 19

The unsubstituted glycoluril dimer (136 mg, 0.44 mmol), the diether of 3a-(p-iodophenyl)-6a-methylglycoluril (compound 1.2 where X=I) (264 mg, 0.62 mmol) and concentrated hydrochloric acid (1 mL) were ground together. The mixture was heated to 110°C for 2-3 hr. Methanol was added to the hot mixture and cooled. The precipitate was collected by filtration. Purification on Sephadex SP gave the  $\alpha,\delta$ -di(p-iodophenyl)dimethylcucurbit[2,4]uril as the major product.

## Example 20

The unsubstituted glycoluril dimer (compound 2.2) (1 g, 3.3 mmol) and the tetrol (compound 2.6) of 3a,6a-cyclopentanoglycoluril (1 g, 3.3 mmol) were ground together as a fine powder and added to concentrated hydrochloric acid (12 mL). The mixture was stirred at room temperature for 1 hr. The mixture was heated to 100°C for 2-3 hr. Evaporation of the acid in vacuo gave  $\alpha,\delta$ -dicyclopentanocucurbit[2,4]uril as the major product, 80%.

## Example 21

The unsubstituted glycoluril dimer (compound 2.2) (135 mg, 0.44 mmol) and LiCl (9 mg) were added to conc HCl (10 mL) and stirred at room temperature for 20 min. A mixture of the diether (compound 2.5) of dimethylglycoluril (55.9 mg, 0.22 mmol) and the diether (compound 1.2 where X=H) of 3a-phenyl-6a-methylglycoluril (140 mg, 0.22 mmol) ground together as a homogeneous solid, were added to the mixture. After an initial period of 20 min at room temperature the mixture was heated to 100°C for 3 hr. Evaporation of the acid in vacuo gave  $\alpha$ -phenyl- $\alpha$ -methyl- $\delta$ -dimethylcucurbit[2,4]uril as the major product.

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## Example 22

The formaldehyde diether derivative of 3a,6a-diphenylglycoluril (2.9 g, 7.7 mmol), the unsubstituted glycoluril dimer (compound 2.2) (4.7 g, 15.4 mmol) and  
5  $K_2CO_3$  (530 mg) were mixed together in methanesulfonic acid (40 mL) at room temperature, 20 min then 10 min at 50°C. Then paraformaldehyde (460 mg) was added and the mixture heated to 100°C for 2.5 hr. The cooled homogeneous mixture was poured into MeOH (170 mL) and the product collected by  
10 filtration washed MeOH and dried to give 7.6 g of product mixture, predominantly diphenylcucurbit[1,4]uril.

## Example 23

A mixture of compound 1.12 (500 mg, 2.2 mmol) and  
15 paraformaldehyde (295 mg) was heated under reflux in trifluoroacetic acid (10 mL) for several hours. The product obtained by evaporation of the solvent was used without purification. The product was mixed with the glycoluril dimer (compound 2.2) (670 mg) and 7M HCl (15  
20 mL) was added at ambient temperature. After 30min the mixture was heated to 90°C for 3h. The mixture was then cooled and methanol added to precipitate the product.  $^1H$  NMR showed characteristic cucurbituril proton resonances as groups of doublets at 4.1 and 5.1ppm, in addition the  
25 methyl proton resonances were evident at 2.3 ppm. Dioxane binding showed that a cucurbit[6]uril had been formed. The cucurbit[6]uril contained some units of the formula (B) in which one of the  $R^3$  groups is  $=C(COCH_3)_2$ .

## 30 Example 24

A mixture of glycoluril dimer (compound 2.2) (1.2 g, 3.9 mmol), the diether (compound 2.5) of dimethylglycoluril (1 g, 3.9 mmol) and LiCl (250 mg) were ground together to give a fine powder. To this mixture was added concentrated  
35 HCl (10 ml) and the mixture stirred at ambient temperature for 1 hr. To this mixture was added the trimer compound 2.4 (1.95 g, 3.9 mmol) and stirring continued for an

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additional hr. The mixture was then heat to 100°C for 3  
hr. The solvent was evaporated in vacuo to give a solid  
residue, which was purified on Dowex cation exchange  
resin. Alpha, gamma, zeta-hexamethylcucurbit[3,4]uril was  
5 isolated as a crystalline solid 1.1 g.

The present invention can be used to prepare cucurbiturils  
having particular R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> groups at particular  
relative locations in the units of the formula (B) making  
10 up the cucurbituril. This allows the preparation of  
cucurbiturils having suitable solubility and complexing  
properties for the intended use of the cucurbituril, or  
having particular numbers and relative locations of  
substituents for reaction with other compounds.

15 As is apparent from the above examples, the method of the  
present invention can produce good yields of specific  
cucurbiturils, including specific variably substituted  
cucurbiturils. The prior art methods for producing a  
20 variably substituted cucurbituril typically result in the  
production of a large number of different cucurbiturils,  
and thus typically low yields of the desired variably  
substituted cucurbituril.

25 In some embodiments of the present invention, the method  
of the present invention produces a mixture of different  
cucurbiturils. If required, individual cucurbit[4 to  
12]urils prepared by the method of the present invention  
may be separated from any other cucurbit[4 to 12]urils  
30 produced by the reaction, by the separation methods  
described in WO 00/68232.

The potential uses for cucurbit[n]urils prepared by the  
method of the present invention are large, with academic,  
35 industrial, analytical and pharmaceutical applications.  
As a class, cucurbit[n]urils can be favourable compared to  
the cyclodextrins because both molecular systems possess a

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hydrophobic cavity with polar end caps. Cucurbiturils are however thermally more robust than cyclodextrins and are stable to strong acid solutions unlike cyclodextrins. Cyclodextrins have been used in a wide range of applications including slow release drugs, odour entrapment agents in plastic films, and enzymimics for synthesis. It is believed that cucurbit[n]urils will be of use in similar areas where benefit can be taken of the ability of the cucurbit[n]urils to take up molecules or compounds into their central cavity or bind molecules at the polar ends of the cavity. Such uses include:

Environmental (water, soil and air)

- Remediation, by the binding of polluting products and their removal.
- Preventative, e.g. by binding of potential pollutants before wastes are released to the environment.
- Uses in biodegradable polymers.

Domestic and Public

- Incorporation into polymers as odourisers, releasing fragrances slowly over time.
- Incorporated into polymers to trap unpleasant odours or toxic vapours.
- Encapsulation of bleaching and whitening agents.

Food

- Flavour enhancers.
- Flavour optimisers (hiding unpleasant flavours).
- Polyphenol removal to reduce discolouration of juices.

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Pharmaceutical

- Slow release drugs, limiting side effects and reducing the frequency of doses.
- 5   ▪ Increasing drug stability in vivo or on the shelf.
- Detoxification, for example, decreasing stomach irritations, or the treatment of chemical allergens by encapsulation.

10   Agricultural/horticultural

- Slow release of herbicides and pesticides.
- Stabilisation of agricultural chemicals against light and heat.

15

Manufacturing

- Enzyme/catalyst mimics.
- Regioselective control over reaction products.
- 20   ▪ Manipulation of paint and polymer products.
- Chromatographic columns for chemical purification.
- Analytical tools and devices.
- Printing and photography.

25   Those skilled in the art will appreciate that the invention described herein may be susceptible to variation and modifications other than those specifically described or exemplified. It is to be understood that the present invention encompasses all such variations and  
30   modifications that fall within its spirit and scope.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary  
35   implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but

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not to preclude the presence or addition of further features in various embodiments of the invention.

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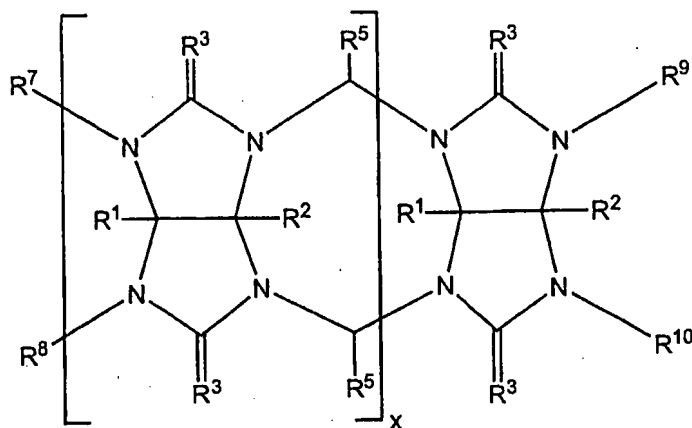
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## CLAIMS

1. A method for preparing a cucurbit[n]uril, the method comprising the steps of:

5 (a) mixing

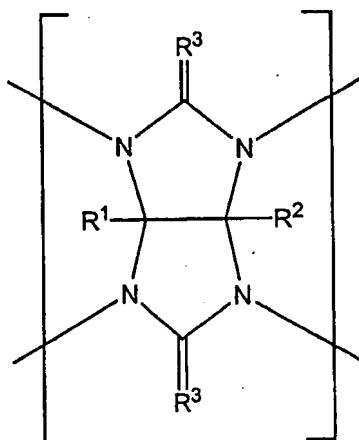
(1) a compound of the formula (1)



(1)

10 wherein:

for each unit of the formula (A)



(A)

15 in the compound,

R¹ and R² may be the same or different and are each a univalent radical, or

R¹, R² and the carbon atoms to which they are bound

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together form an optionally substituted cyclic group, or  $R^1$  of one unit of the formula (A) and  $R^2$  of an adjacent unit of the formula (A) together form a bond or a divalent radical, and

- 5 each  $R^3$  is independently selected from the group consisting of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, where Z is an electron withdrawing group, X is halo and R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical;

each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;

- 15  $R^7$  and  $R^8$  may be the same or different and are independently selected from the group consisting of H and -CHR<sup>5</sup>OR<sup>5</sup>, or  $R^7$  and  $R^8$  together form the group -CHR<sup>5</sup>-O-CHR<sup>5</sup>-, where each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;

- 20  $R^9$  and  $R^{10}$  may be the same or different and are independently selected from the group consisting of H and -CHR<sup>5</sup>OR<sup>5</sup>, or  $R^9$  and  $R^{10}$  together form the group -CHR<sup>5</sup>-O-CHR<sup>5</sup>-, where each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl; and

x is an integer from 1 to 10;

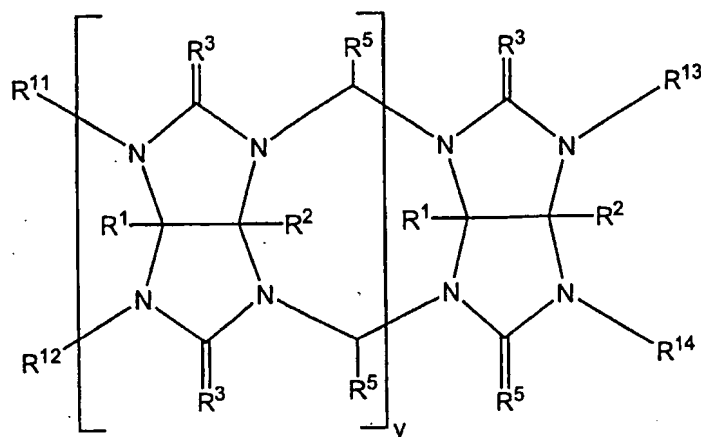
(2) one or more compounds of the formula (2)

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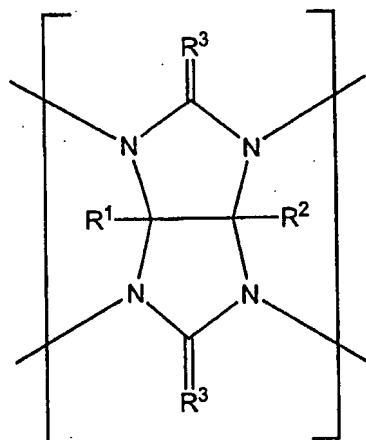


(2)

wherein:

for each unit of the formula (A)

5



(A)

in the compound,

 $R^1$  and  $R^2$  may be the same or different and are each a

10 univalent radical, or

 $R^1$ ,  $R^2$  and the carbon atoms to which they are bound together form an optionally substituted cyclic group, or $R^1$  of one unit of the formula (A) and  $R^2$  of an adjacent unit of the formula (A) together form a bond or a divalent

15 radical, and

each  $R^3$  is independently selected from the group consisting of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, where Z is an electron withdrawing group, X is halo and R is H, an optionally



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substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical;

- 5 each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;

- $R^{11}$  and  $R^{12}$  may be the same or different and are independently selected from the group consisting of H and  
10  $-\text{CHR}^5\text{OR}^5$ , or  $R^{11}$  and  $R^{12}$  together form the group  $-\text{CHR}^5\text{-O-CHR}^5-$ , where each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;

- $R^{13}$  and  $R^{14}$  may be the same or different and are  
15 independently selected from the group consisting of H and  $-\text{CHR}^5\text{OR}^5$ , or  $R^{13}$  and  $R^{14}$  together form the group  $-\text{CHR}^5\text{-O-CHR}^5-$ , where each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl; and

- 20 y is 0 or an integer from 1 to 9 and  $x + y = 10$  or less; and

(3) an acid;

to form a mixture;

- 25 and

(b) exposing the mixture to conditions effective for the compound of the formula (1) and the one or more compounds of the formula (2) to form a cucurbit[n]uril.

- 30 2. A method according to claim 1 wherein  $R^1$  and  $R^2$  are independently selected from the group consisting of  $-\text{R}$ ,  $-\text{OR}$ ,  $-\text{NR}_2$  where each R is independently selected,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  $-\text{X}$ ,

- 35  $-\text{COR}$ ,  $-\text{COX}$ ,  $-\text{COOR}$ ,  $-\text{CR}_2$  where each R is independently

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selected,  $\begin{array}{c} \text{NR} \\ || \\ -\text{C}-\text{R} \end{array}$  where each R is independently selected,

5 -SeR, -SiR<sub>3</sub> where each R is independently selected, -SR,

-SOR,  $\begin{array}{c} \text{O} \\ || \\ -\text{S}-\text{O}-\text{R} \\ || \\ \text{O} \end{array}$ , -SO<sub>2</sub>R, -S-S-R, -BR<sub>2</sub> where each R is

10

independently selected, -PR<sub>2</sub> where each R is independently selected,

15  $\begin{array}{c} \text{O} \\ || \\ -\text{P}-\text{O}-\text{R} \\ | \\ \text{OR} \end{array}$  where each R is independently selected,  $\begin{array}{c} \text{O} \\ || \\ -\text{P}-\text{NR}_2 \\ | \\ \text{NR}_2 \end{array}$

where each R is independently selected, -P<sup>+</sup>R<sub>2</sub> where each R is independently selected and a metal or metal complex,

20

wherein R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and X is halo.

25

3. A method according to claim 2 wherein R is H, an optionally substituted C<sub>1-10</sub> alkyl, an optionally substituted C<sub>2-10</sub> alkenyl, or an optionally substituted C<sub>5-10</sub> aryl.

30

4. A method according to any one of claims 1 to 3 wherein the mixture further comprises one or more compounds that can form bridges of the formula -CHR<sup>5</sup>- between compounds of formula (1) and (2).

35

5. A method according to claim 4 wherein the compound that can form bridges of the formula -CHR<sup>5</sup>- between

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compounds of formula (1) and (2) is selected from the group consisting of trioxane, optionally substituted 2,3-dihydropyran, optionally substituted 2,3-dihydrofuran, compounds of the formula  $R^5COR^5$  and compounds of the formula  $R^5OC(R^5)_2OR^5$ , where each  $R^5$  is independently selected and is H, alkyl or aryl.

6. A method according to claim 5 wherein the compound that can form bridges of the formula  $-CHR^5-$  between compounds of formula (1) and (2) is formaldehyde, paraformaldehyde or trioxane.

7. A method according to any one of claims 1 to 6 wherein step (b) comprises heating the mixture to a temperature of from 20°C to 120°C for a period of time sufficient for the compound of formula (1) and the one or more compounds of formula (2) to form a cucurbit[n]uril.

8. A method according to any one of claims 1 to 7 wherein  $R^7 = R^8$ ,  $R^9 = R^{10}$ ,  $R^{11} = R^{12}$  and  $R^{13} = R^{14}$ .

9. A method according to any one of claims 1 to 8 wherein Z is selected from the group consisting of  $-NO_2$ ,  $-CO_2R$ ,  $-COR$ ,  $-CN$  and  $-CX_3$ , where X is halo and R is H, alkyl, alkenyl, alkynyl, aryl, or saturated or unsaturated heterocyclyl.

10. A method according to any one of claims 1 to 9 wherein  $R^3$  is =O.

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11. A method according to any one of claims 1 to 10 wherein  $R^5$  is H.

12. A method according to any one of claims 1 to 11 wherein the mixture further comprises a templating compound.

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13. A method according to claim 12 wherein the templating compound is a salt.

14. A method according to claim 13 wherein the anion of the salt corresponds to the anion of the acid in the mixture.

15. A method according to claim 12 wherein the templating compound is selected from ammonium chloride, lithium chloride, sodium chloride, potassium chloride, rubidium chloride, caesium chloride, ammonium bromide, lithium bromide, sodium bromide, potassium bromide, rubidium bromide, caesium bromide, lithium iodide, sodium iodide, potassium iodide, rubidium iodide, caesium iodide, potassium sulfate, lithium sulfate, tetrabutylammonium chloride, tetraethylammonium chloride, o-carborane, thioacetamide, N-(1-naphthyl) ethylenediamine, 2,2'-biquinoline, p-bromoaniline, taurine, blue tetrazolium, 2-amino-3-methyl benzoic acid, indol-3-aldehyde, cysteine, 4-acetamidoaniline, p-aminophenol, acetamide, 4-aminoacetophenone, 4-dimethylaminobenzaldehyde, 2-aminobenzimidazol, bis-(4,4'-bipyridyl)- $\alpha,\alpha'$ -xylene, red phosphorus, and lithium p-toluenesulfonate.

16. A cucurbit[n]uril prepared by the method of any one of claims 1 to 15.

17. A compound of any of the following formulas 1.1 to 1.10:

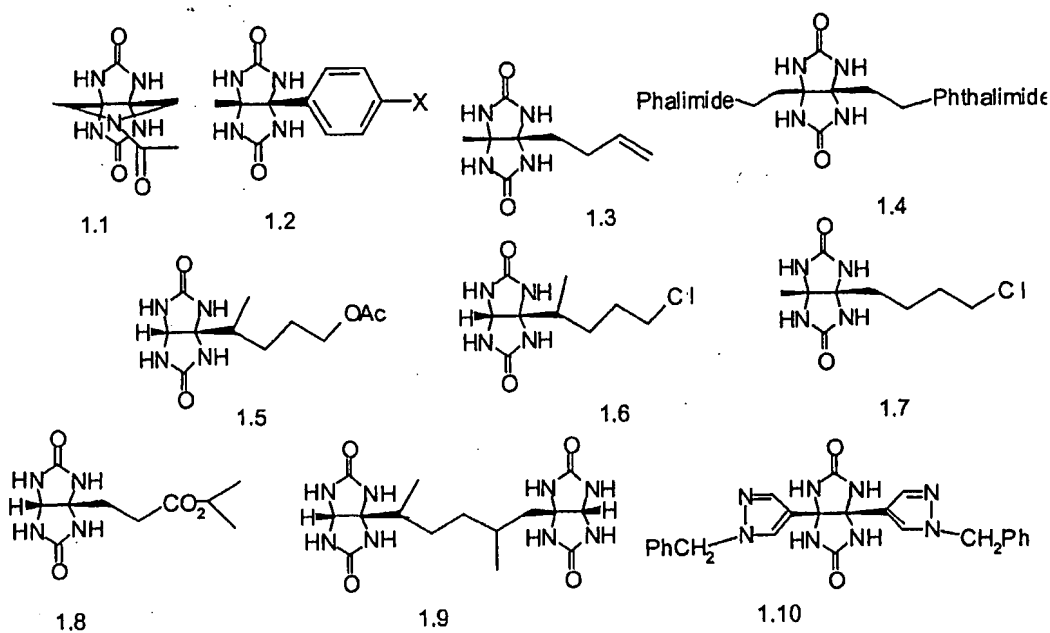
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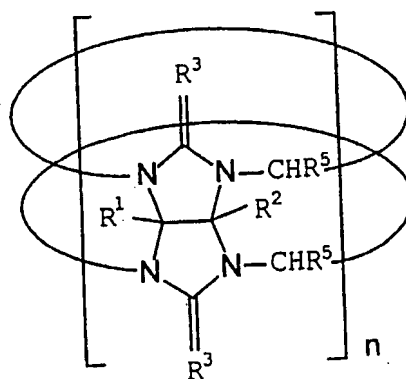


wherein in formula 1.2, X is halo.

5 18. A cucurbit[n]uril of the formula:

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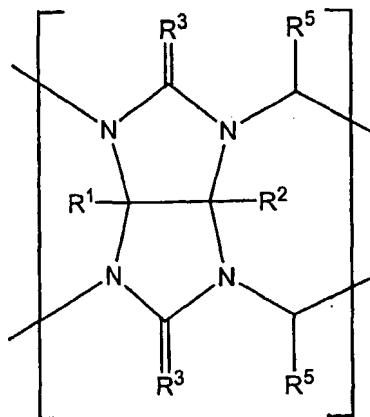
wherein:

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for each unit of the formula (B):



(B)

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in the cucurbit[n]uril,

$R^1$  and  $R^2$  may be the same or different and are each a univalent radical, or

10  $R^1$ ,  $R^2$  and the carbon atoms to which they are bound together form an optionally substituted cyclic group, or  $R^1$  of one unit of the formula (B) and  $R^2$  of an adjacent unit of the formula (B) together form a bond or a divalent radical,

each  $R^3$  is independently selected from the group consisting  
15 of =O, =S, =NR, =CXZ, =CRZ and =CZ<sub>2</sub>, wherein Z is an electron withdrawing group, X is halo and R is H, an optionally substituted straight chain, branched or cyclic, saturated or unsaturated hydrocarbon radical, or an optionally substituted heterocyclyl radical, and

20 each  $R^5$  is independently selected from the group consisting of H, alkyl and aryl;  
and n is an integer from 4 to 12,

and wherein at least one  $R^3$  in the cucurbit[n]uril is =CXZ,  
25 =CRZ or =CZ<sub>2</sub>.

19. A cucurbit[n]uril according to claim 17 wherein Z is selected from the group consisting of -NO<sub>2</sub>, -CO<sub>2</sub>R, -COR, -CN

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and  $-CX_3$ , and X is halo.

20. A cucurbit[n]uril according to claim 17 or 18 wherein  
at least one  $R^3$  in the cucurbit[n]uril is  $=C(CN)COCH_3$  or  
5  $=C(COCH_3)_2$ .

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU2004/001232

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. <sup>7</sup>: C07D 487/04, 487/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN structure search of claims 17 and 18 on chemical abstracts.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 094 065 B1 (POHANG UNIVERSITY OF SCIENCE AND TECHNOLOGY FOUNDATION) 25 April 2001 See especially claims 7, 13	1
X	WO 2000 068232 A (UNISEARCH LIMITED) 16 November 2000 See especially pages 6, 7, 11	1
X	WO 2003 055888 A (POSTECH FOUNDATION) 10 July 2003 See especially claims 9, 13	1
X	DAY, A. et al, "Controlling factors in the synthesis of cucurbituril and its homologues", J. Org. Chem. (2001), Vol. 66, pp. 8094-8100	1
X	See entire document	1

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date, but later than the priority date claimed	

Date of the actual completion of the international search  
5 November 2004

Date of mailing of the international search report  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2004/001232

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE, J. W. et al, "Cucurbituril homologues and derivatives: new opportunities in supramolecular chemistry", Accounts of Chemical Research (2003), Vol. 36, pp.621-630  See especially schemes 2, 6, 7.	1
X	KIM, J et al, "New cucurbituril homologues: syntheses, isolation, characterization, and X-ray crystal structures of cucurbit[n]uril (n= 5, 7, and 8)", J. Am. Chem. Soc (2000), Vol. 122, pp. 540-541  See entire document	1
X	ISOBE, H. et al, "Synthesis of disubstituted cucurbit[6]uril and its rotaxane derivative", Organic Letters (2002), Vol. 4, No. 8, pp.1287-1289  See abstract and scheme atop right column p.1288	1

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU2004/001232

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
EP	1 094 065	DE	60007257	JP	3432483
		US	6365734	US	6639069
		US	2004039195	JP	2001122877
WO	2000 068232	AU	43851/00	US	2002133003
		CA	2373159	CN	1355803
		EP	1181293	US	6793839
WO	2003 055888	US	2003140787	JP	2002544133
		CA	2468801	EP	1463732
		EP	1463732	KR	2003060053

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX